REMARKS

Claims 15-17 and 22-31 were pending in the application. Claims 24 and 26-29 have been canceled as being directed to a non-elected invention. Claims 22, 30 and 31 have also been canceled, without prejudice. Claim 15 has been amended and new claims 32, 33, and 34 have been added. Accordingly, after entry of the present amendments, claims 15-17, 23, 25, and 32-34 will be pending. Support for the amendments to the claims and the newly added claims can be found throughout the specification including originally filed claims.

No new matter has been added. Any amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to more particularly point out and distinctly claim Applicants' invention in order to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

References Cited in Information Disclosure Statement Filed on January 22, 2001

The Examiner has stated that "[t]he references cited in the PTO-1449 form filed January 29, 2001 have not been considered since no reference is provided."

Applicants respectfully submit that, as set forth in the Information Disclosure Statement filed on January 22, 2001, the present application is a Divisional Application of U.S. Serial No. 09/469,636, filed December 22, 1999, now U.S. Patent No. 6,444,873 (Atty. Docket No. AHN-001). All references listed on the PTO Form 1449 have been previously cited by or submitted to the Office in the prior application, and, in accordance with 37 C.F.R. §1.98(d), copies of these references are not required to be submitted with the Information Disclosure Statement. However, for the Examiner's convenience, Applicants have included copies of each of the references listed on the PTO Form 1449 (references A1-B9) herewith. A copy of the PTO Form 1449 is also included herewith. In light of the above, Applicant respectfully requests that these references (references A1-B9) now be considered by the Examiner.

Rejection of Claims 15-17, 22, 23, 30, and 31 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 15-17, 22, 23, 30 and 31 under 35 U.S.C. 112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." In particular, the Examiner is of the opinion that

> [t]he instant specification fails to provide a written description of what a small molecule that has a function of modulating MSH5 expression would be. Throughout the instant specification, only three places mention the term "small molecules" (page 8, line 5, page 14, line 32, and page 15, line 23). No small molecules are exemplified. In fact, there is only description of what the small molecules can do (i.e., modulating the expression of MSH5) and no description of what these small molecules are.

Applicants respectfully traverse the instant rejection. Applicants respectfully submit that the description of Applicants specification and the fact that there was a well established meaning to the term "small molecule", a skilled artisan would be informed that Applicants were in possession of the claimed invention at the time the application was filed. In order to meet the written description requirement of the first paragraph of 35 U.S.C. §112, it is not necessary that a patent specification describe each and every specific member of a genus recited in a claim.

One of ordinary skill in the art would recognize the meaning of the term "small molecule" as including chemical entities which are not oligonucleotides, not DNA or RNA, not peptides, and not proteins (as set forth in the Interview Summary prepared by Examiner C. Low, Paper No. 14, for the instant application). Applicants specification describes entire libraries which contain small molecules, *e.g.,* spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the one-bead one-compound' library method; and synthetic libraries (see page 15, lines 5-14 of Applicants specification). These libraries of small molecules are described in Lam *et al.* (1997) *Anti-Cancer Drug Design* 12:145-167, a copy of which is attached hereto as Appendix B. The Lam *et al.* reference is expressly incorporated into Applicants specification. Lam *et al.* specifically describes small molecules contained within libraries (see, for example Figure 1

at page 147). These libraries are distinguished from peptide, oligonucleotide, and oligosaccharide libraries.

Furthermore, Applicants respectfully submit that, as set forth in the Written Description Guidelines at page 4, "the absence of definitions or details for well-established terms or procedures should not be the bases of a rejection under 35 U.S.C. 112, first paragraph. The term "small molecule" was a well-established term at the time of filing the instant application. As evidence that the term "small molecule" was well-established at the time the instant application was filed, Applicants submit herewith a copy of U.S. Patent No. 5,846,722 (Appendix C; issued on December 8, 1998) and U.S. Patent No. 5,693,476 (Appendix D; issued on December 2, 1997). U.S. Patent No. 5,846,722 contains claims directed to methods for determining whether an agent and a target protein interact using an agent/ligand complex comprising a small molecule agent. Furthermore, U.S. Patent No. 5,693,476 contains claims directed to methods for identifying a compound capable of affecting binding of a SNAP-25 alpha-SNAP, n-sec1 or VAMP synaxtin-binding protein (SBP) with a corresponding binding protein binding site (BPBS) from a region of synaxtin, in the presence and absence of a test compound, where the test compound may be one of a plurality of small molecules in a small molecule combinatorial library. Accordingly, the term "small molecule" was well-established in the art at the time of filing of the instant application.

In light of the well-established nature of the term "small molecule" as well as the description in applicants specification of small molecules and libraries containing small molecules, Applicants respectfully submit that the specification provides sufficient written to inform a skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 22, 23, 30, and 31 Under 35 U.S.C. §112, First Paragraph

The Examiner has also rejected claims 22, 23, 30 and 31 under 35 U.S.C. 112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly

connected, to make and/or use the invention." In particular, the Examiner cites the *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 .

Applicants respectfully traverse. However, in the interest of expediting prosecution and in no way acquiescing to the Examiner's rejection, claims 22, 30, and 31 have been canceled, thereby rendering the foregoing rejection moot as it pertains to these claims. With respect to claim 23, the above quoted rejection is respectfully traversed on the grounds that the present specification does provide adequate guidance which would enable the ordinarily skilled artisan to make and use the claimed invention without undue experimentation.

Claim 15 is directed to methods for modulating fertility in a subject comprising contacting MSH5 or a cell expressing MSH5 with a compound in an amount sufficient to modulate MSH5 expression or activity, thereby modulating fertility in a subject. Claim 23 is directed to modulating fertility in a subject comprising contacting MSH5 or a cell expressing MSH5 with a compound, *e.g.,* a small molecule, which modulates MSH5 expression. Applicants' specification teaches that animals which are homozygous for a null mutation in MSH5 are sterile. Furthermore, Applicants have demonstrated in the present application and in subsequent publications (Kneitz B. *et al.* (2000) *Genes Dev.* 14(9):1085-97, provided herewith as Appendix E) that MSH5 is essential for proper chromosome pairing during mammalian meiosis. Therefore, inhibiting MSH5 expression or activity by contacting MSH5 or a cell expressing MSH5 inhibits chromosome pairing during meiosis and is therefore useful in contraception.

In particular, the Examiner is of the opinion that

> [t]he specification and claims do not disclose one reasonable method for the utilization of the small molecule compounds that encompasses numerous and unpredictable variant molecules to modulate MSH5 activities and expression in cell and to target MSH5-related infertility. Moreover, the instant claims do not disclose characteristics/attribute of the MSH5 activity that is fundamentally important for the modulation by MSH5 interacting compound(s). Thus, employing numerous and unpredictable candidate compounds to target undisclosed MSH5 "activity" would result in encompassing all possible approaches of modulation of MSH5 function and expression and related fertility disorder thereby.

Furthermore, the Examiner is of the opinion that

> [t]he disclosure lacks guidance/direction as to (i) how to ascertain suitable small molecule compounds used in the herein claimed invention, (ii) what

MSH5 activities is/are affected, (iii) with respect to any combination of (i) and (ii), how MSH5 expression of MSH5 per se is regulated with reasonable outcome without undue experimentation.

Applicants respectfully submit that the pending claims require modulating MSH5 expression or activity. Applicants' specification is enabling for identifying compounds which modulate MSH5 expression or activity. One of skill in the art would easily be able to utilize the screening assays described in Applicants' specification to identify suitable compounds which modulate MSH5 expression or activity (see, for example, page 15, lines 4-14), without undue experimentation. As set forth above, libraries which may be screened for small molecules which modulate MSH5 expression or activity were described in Applicants' specification and were well known by a person of ordinary skill in the art at the time of filing. One of skill in the art would also be able to contact MSH5 or a cell expressing MSH5 with the identified compound and measure modulation, *e.g.,* inhibition, of MSH5 activity or expression, using methods well known to one or ordinary skill in the art at the time of filing. For example, modulation of MSH5 expression may be measured by, for example, quantitative PCR, Northern analysis, *in situ* hybridization. Techniques for detection and quantification of MSH5 protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence, all of which were known to one of skill in the art at the time of filing the instant application. Assays for measuring modulation of the activity of MSH5 include assays for measuring modulation of any known activity of an MSH5 peptide. For example, as set forth in Applicants' specification at page 1, lines 12-20, MSH5 is known to be involved in DNA mismatch repair (see Modrich, *et al.* (1996) *Ann Rev Biochem* 65, 101-133 and Kolodner (1996) *Genes Dev.* 10, 1443-1442, the contents of which were incorporated into Applicants' specification at page 16, lines 11-14. Furthermore, Applicants have demonstrated in the present application and in subsequent publications (page 20, line 28 of Applicants' specification and Kneitz B. *et al.* (2000) *Genes Dev.* 14(9):1085-97, provided herewith as Appendix E) that MSH5 is essential for proper chromosome pairing during mammalian meiosis.

Moreover, Applicants' specification provides working examples with teach that ablation of the MSH5 gene in transgenic animals causes infertility in these animals (see Example 1). Working examples are also provided which teach methods for modulating MSH5 expression or

activity (see page 17, lines 16-28). In combination with the teachings as set forth above of identifying compounds which modulate MSH5 expression or activity, Applicants specification provides adequate enablement for one of ordinary skill in the art to carry out the claimed invention without undue experimentation. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 15-17, 22, 23, 30, and 31 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 15-17, 22, 23, 30 and 31 under 35 U.S.C. 112, second paragraph, as being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner is of the opinion that "[t]he expression "compound" in claim 15 renders the claim indefinite as to what compounds are encompassed by the claims. Only functional language is recited. Therefore, one of ordinary skill in the art would not know what compounds are or not fall into the scope of the herein claims."

Applicants respectfully traverse the foregoing rejection. Applicants respectfully submit that the claim language is clear and definite and would be understood by one of skill in the art when read in combination with the teachings of the specification. Claim 15 is directed to methods for modulating fertility in a subject comprising contacting MSH5 or a cell expressing MSH5 with a compound in an amount sufficient to modulate MSH5 expression or activity, thereby modulating fertility in a subject. Applicants' specification clearly describes compounds which modulate MSH5 expression or activity. For example, the specification defines test compounds as peptides, peptidomimetics, small molecules or other drugs which "bind to MSH5 proteins, or have a stimulatory or inhibitory effect on, for example, the expression or activity of an MSH5 substrate." Accordingly, a compound as used in the methods of the invention includes any compound which modulates MSH5 activity or expression. As set forth in M.P.E.P. 2173, "[b]readth of a claim is not to be equated with indefiniteness." The scope of the claimed subject matter is clear. Accordingly, the pending claims comply with 35 U.S.C. 112, second paragraph.

For the reasons set forth above, Applicants submit that the claimed invention is clear and definite. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

The Examiner is also of the opinion that "[t]he expression "sufficient concentration" in claim 15 renders the claims indefinite because the activity of MSH5 that is modulated is not clear to one of ordinary skill in the art. Therefore, it is not clear what concentration would be encompassed by the term "sufficient concentration"."

Applicants respectfully traverse the foregoing rejection. Applicants respectfully submit that the pending claims are clear and definite in view of the teachings of Applicants' specification. Claim 15 has been amended so that it no longer recites the phrase "sufficient concentration." Claim 15 is directed to methods for modulating fertility in a subject comprising contacting MSH5 or a cell expressing MSH5 with a compound in an amount sufficient to modulate MSH5 expression or activity, thereby modulating fertility in a subject. The amount of compound which would be encompassed by the claim includes any amount which is capable of modulating MSH5 expression or activity.

As set forth above, modulation of MSH5 expression or activity may be measured by any one of many assays known to one or ordinary skill in the art at the time the application was filed. Modulation of MSH5 expression may be measured by, for example, quantitative PCR, Northern analysis, *in situ* hybridization. Techniques for detection and quantification of MSH5 protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence, all of which were known to one of skill in the art at the time of filing the instant application. Assays for measuring modulation of the activity of MSH5 include assays for measuring modulation of any known activity of an MSH5 peptide. For example, as set forth in Applicants' specification at page 1, lines 12-20, MSH5 is known to be involved in DNA mismatch repair (see Modrich, *et al.* (1996) *Ann Rev Biochem* 65, 101-133 and Kolodner (1996) *Genes Dev.* 10, 1443-1442, the contents of which were incorporated into Applicants' specification at page 16, lines 11-14. Furthermore, Applicants have demonstrated in the present application and in subsequent publications (see page 20, line 28 of Applicants' specification and Kneitz B. *et al.* (2000) *Genes Dev.* 14(9):1085-97, provided herewith as Appendix E) that MSH5 is essential for proper chromosome pairing during mammalian meiosis.

Based on the foregoing, claim 15 is clear and definite based on the teachings of Applicants' specification. Accordingly Applicants' respectfully request reconsideration and withdrawal of the foregoing rejection.

Furthermore, the Examiner is of the opinion that "[c]laim 22 is indefinite because it recites "said compound is a contraceptive agent", in which the said agent is neither disclosed in the specification nor in the claims and referred to [as] any agent having activity that can be served as contraceptives."

Applicants respectfully traverse the foregoing rejection. However, in an effort to expedite prosecution of the instant application, and in no way acquiescing to the Examiner's rejection, Applicants have canceled claim 22, thereby rendering the aforementioned rejection moot.

Lastly, the Examiner is of the opinion that "[t]he term "small molecules" in claim 25 is a relative term which renders the claim indefinite. The term "small molecules" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention."

Applicants respectfully traverse the foregoing rejection. Applicants respectfully submit that the claim language is clear and definite and would be understood by one of skill in the art when read in combination with the teachings of the specification. Claim 25 is directed to *in vivo* methods for modulating MSH5 expression or activity comprising contacting MSH5 or a cell expressing MSH5 with a compound in an amount sufficient to modulate MSH5 expression or activity, wherein the compound is a small molecule. The meaning of the term "small molecule" would have been readily apparent to one of ordinary skill in the art at the time the instant application was filed in view of the teachings of Applicants' specification and the well established meaning of the term. A small molecule is understood by one of ordinary skill in the art to mean chemical entities which are not oligonucleotides, not DNA or RNA, not peptides, and not proteins (as set forth in the Interview Summary prepared by Examiner C. Low, Paper No. 14, for the instant application). Applicants specification describes entire libraries of compounds which contain small molecules, *e.g.,* spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the one-bead one-compound' library method; and synthetic libraries (see page 15, lines 5-14 of Applicants specification). These libraries of small molecules are described in Lam *et al.* 1997) *Anti-Cancer Drug Design* 12:145-167, a copy of which is attached hereto as Appendix B. The Lam *et al.* reference is

expressly incorporated into Applicants specification. Lam *et al.* specifically describes small molecules contained within libraries (see, for example Figure 1 at page 147). These libraries are distinguished from peptide, oligonucleotide, and oligosaccharide libraries. Furthermore, as evidence that the term "small molecule" would have been apparent to one of ordinary skill in the art at the time the application was filed, Applicants submit herewith U.S. Patent No. 5,846,722 (Appendix C; issued on December 8, 1998) and U.S. Patent No. 5,693,476 (Appendix D; issued on December 2, 1997). U.S. Patent No. 5,846,722 contains claims directed to methods for determining whether an agent and a target protein interact using an agent/ligand complex comprising a small molecule agent. Furthermore, U.S. Patent No. 5,693,476 contains claims directed to methods for identifying a compound capable of affecting binding of a SNAP-25 alpha-SNAP, n-sec1 or VAMP synaxtin-binding protein (SBP) with a corresponding binding protein binding site (BPBS) from a region of synaxtin, in the presence and absence of a test compound, where the test compound may be one of a plurality of small molecules in a small molecule combinatorial library. Accordingly, the meaning of the term "small molecule" was well-established in the art at the time of filing of the instant application and it's meaning readily apparent. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 15, 16, and 31 Under 35 U.S.C. §102(e)

The Examiner has rejected claims 15, 16, and 31 under 35 U.S.C. 102(e) as being anticipated by Fishel *et al.* (U.S.P.N. 6,333,153). According to the Examiner, "Fishel *et al.* teaches a process for modulating MSH5 protein activity by a binding solution comprising ATP and ADP, in a specific concentration, that can affect the activity of MSH5 (See col. 20, line 33 - col. 21, line 10)."

Applicants respectfully traverse the foregoing 35 U.S.C. §102e rejection. For a prior art reference to anticipate a claimed invention in terms of 35 U.S.C. §102, the prior art must teach ***each and every element*** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Applicants respectfully submit that Fishel *et al.* fail to teach each and every element of the pending claims. Claim 15 is directed to methods for modulating fertility in a subject comprising contacting MSH5 or a cell expressing MSH5 with a compound in an amount

sufficient to modulate MSH5 expression or activity, thereby modulating fertility in a subject. Claim 16 is directed to the method of claim 15, where the expression or activity of MSH5 is inhibited. New claim 32 is directed to methods for inhibiting MSH5 expression or activity in a subject comprising administering to said subject an effective amount of an inhibitor of MSH5 expression or activity. New claim 33 is directed to methods for preventing fertilization in a subject by administering to said subject an effective amount of an inhibitor of MSH5 expression or activity, thereby preventing fertilization in a subject. New claim 34 is directed to methods for modulating meiosis in a subject comprising administering to said subject an effective amount of an inhibitor of MSH5 expression or activity, thereby modulating meiosis in a subject.

The Fishel *et al.* reference is concerned with modifying a mismatched DNA using a MutS homolog dimer. The methods described by Fishel *et al.* relate to binding a MutS homolog dimer, *e.g.,* an MSH dimer, to the mismatched DNA in the presence of a binding solution comprising ADP, where the MutS dimer binds ADP and the ADP-bound MutS dimer associated with the mismatched region of the DNA.

Fishel *et al.* do not teach or suggest any association between MutS homologs, such as MSH5, and contraception or meiosis. Neither do Fishel *et al.* teach or suggest methods for modulating fertility in a subject or methods for modulating meiosis in a subject.

Since Fishel *et al.* fail to teach or suggest each and every element of the pending claims this reference does not anticipate the claims. Accordingly, the Examiner is respectfully requested to reconsider and withdraw this section 102(e) rejection.

Rejection of Claims 17, 22, 23, and 30 Under 35 U.S.C. §103

The Examiner has rejected claims 17, 22, 23, and 30 under 35 U.S.C. 103(a) as being "unpatentable over Fishel *et al.* as applied to claims 15-16 above, and further in view of Her et al. (Genomics, 1998;52:50-61) and Baker et al. (Nature Genetics, 1996;13:336-342)."

The Examiner states that "Fishel *et al.* does not expressly teach the inhibition of MSH5 activity would be useful as contraceptive. " Furthermore, the Examiner is of the opinion that "Her et al. teaches structural characterization of human MSH5 gene and suggest that expression of MSH5 and MSH5/MSH4, one of [the functional] heterodimers, in human testis involves in human infertility (See page 59, last paragraph of Discussion Section)." The Examiner is further

of the opinion that "Baker *et al.* teaches the involvement of mouse MLH1 in both DNA mismatch and meiotic crossing over, and speculate that the fertility of MS-2-deficient mice raise the possibility that other MutS-like protein, MSH5, act in conjunction with MLH1 during meiosis (See page 341, col. 1)."

The Examiner is of the opinion that

> [i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the compounds of Fishel et al. to inhibit MSH5 and useful in the method of contraceptive thereby. One of ordinary skill in the art would have been motivated to employ the compounds of Fishel et al. to inhibit MSH5 and useful in the method of contraceptive thereby since MSH5 is involved in meiotic crossing over, which is important in spermatogenesis. Inhibiting such process or the activity thereof, and to reduce the spermatogenesis and employed such method for contraception thereby would be reasonably expected to be effective.

Applicants respectfully traverse the foregoing rejection. To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, *e.g., Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985). ***Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations*** (M.P.E.P. 2143).

Independent claim 15, from which claims 17 and 23 depend, is directed to methods for modulating fertility in a subject comprising contacting MSH5 or a cell expressing MSH5 with a compound in an amount sufficient to modulate MSH5 expression or activity, thereby modulating fertility in a subject. Claim 17 is directed to methods for modulating fertility in a subject comprising contacting MSH5 or a cell expressing MSH5 with a compound, where the compound inhibits MSH5 expression or activity and where the method is used in contraception. Claim 23 is directed to the method of claim 15, where the compound is capable of modulating MSH5 expression. Claim 22 has been canceled, therefore rendering the instant rejection moot as it pertains to this claim.

As set forth above, the Fishel *et al.* reference is generally concerned with modifying a mismatched DNA using a MutS homolog dimer. The methods described by Fishel *et al.* relate to binding a MutS homolog dimer, *e.g.,* an MSH dimer, to the mismatched DNA in the presence of a binding solution comprising ADP, where the MutS dimer binds ADP and the ADP-bound MutS dimer associated with the mismatched region of the DNA.

As set forth above, the primary reference of Fishel *et al.* fails to teach or suggest methods for modulating fertility in a subject comprising contacting MSH5 or a cell expressing MSH5 with a compound in an amount sufficient to modulate MSH5 expression or activity, thereby modulating fertility in a subject. Moreover, the secondary reference of Her *et al.* does not make up for the deficiencies of Fishel *et al.* Specifically, Her *et al.* describe the cloning of the human MSH5 cDNA and amino acid sequence. Her *et al.* state that a "housekeeping gene scenario" is supported for MSH5. Her *et al.* state that MSH5 is expressed in testis, and speculate regarding the ***potential*** involvement of MSH5 in human infertility generally based on expression in testis. Nowhere do Her *et al.* teach or suggest modulating fertility or meiosis or inhibiting MSH5 by contacting MSH5 or a cell expressing MSH5 with a compound, *e.g.,* a small molecule, *in vivo*, as is taught in Applicants' specification. Nor do they teach use of MSH5 in any *in vitro* or *in vivo* assays for modulation of fertility.

The secondary reference of Baker *et al.* also does not make up for the deficiencies of Fishel *et al.* Specifically, Baker *et al.* is directed to the discovery that mice that are deficient in Mlh1 possess microsatellite instability and infertility. Nowhere do Baker *et al.* teach or suggest modulating fertility or meiosis or inhibiting MSH5 by contacting MSH5 or a cell

expressing MSH5 with a compound, *e.g.,* a small molecule, *in vivo*, as is taught in Applicants' specification.

In view of the foregoing, Applicants respectfully submit that the combination of Fishel *et al.* with either Her *et al.* or Baker *et al.* fail to teach or suggest each and every limitation of the claimed invention.

Furthermore, even if the cited art taught all the claim limitations, which Applicants deny, Applicants maintain that at the time the invention was made, the prior art failed to provide sufficient motivation to modify the teachings of the primary references to arrive at the claimed invention. With respect to motivation to make the claimed invention, the Examiner has failed to set forth adequate evidence of a motivating force which would have *impelled* one of ordinary skill in the art to modify the teachings of the references to arrive at the claimed invention. In support of their position, Applicants point to the CAFC decision in *In re Rouffet*, (149 F.3d 1350) (Fed. Cir. 1998)). Rouffet filed a patent application directed to technology to reduce signal transmission and receptor interruptions in the transmission signals from satellites. Rouffet taught changing the shape of the beam transmitted by the satellite's antenna to a fan-shaped beam. The Examiner rejected Rouffet's claims as unpatentable over U.S. patent number 5,199,672 (King) in view of U.S. Patent number 4,872,015 (Rosen) and a report titled "A Novel Non-Geostationary Satellite Communications System" (Ruddy). The CAFC found that:

> [although] the board did not err in finding that the combination of King, Rosen, and Ruddy contains all of the elements claimed in Rouffet's application. . .the Board reversibly erred in determining that one of skill in the art would have been motivated to combine these references in a manner that rendered the claimed invention obvious. Indeed, the Board did not identify any motivation to choose these references for combination.

Similarly, it is Applicants' position that the Examiner has failed to point to any motivation to ***modulate MSH5 expression or activity comprising contacting MSH5 or a cell expressing MSH5 with a compound, e.g., a small molecule***, as presently claimed. In *Rouffet* the Court of Appeals continued:

> [b]ecause the Board did not explain the specific understanding or principle within the knowledge of a skilled artisan that would motivate one with no knowledge of Rouffet's invention to make the combination, this court infers that the examiner selected these references with the assistance of hindsight. This court forbids the use of hindsight in the selection of references that comprise the case of obviousness. See In re Gorman, 933 F.2d 982, 986, 18 U.S.P.Q. 2D (BNA) 1885, 1888 (Fed Cir. 1991). Lacking a motivation to combine references, the Board did not show a proper prima facie case of obviousness. This court reverses the rejection over the combination of King, Rosen, and Ruddy. *In re Rouffet* at [*17].

The Examiner is of the opinion that "[o]ne of ordinary skill in the art would have been motivated to employ the compounds of Fishel *et al.* to inhibit MSH5 and useful in the method of contraception since MSH5 is involved in meiotic crossing over, which is important in spermatogenesis. Inhibiting such process or the activity thereof, and to reduce the spermatogenesis and employed such method for contraception thereby would be reasonably expected to be effective."

Applicants respectfully submit that Her *et al.* disclose that S. cerevisae MSH4 and MSH5 play a role in facilitating crossovers between homologous chromosomes during meiosis and only speculate that human MSH5 could interact with human MSH4 during meiosis. Baker *et al.* also state only that yeast MSH4 and MSH5 play a role in meiotic crossing over. Inhibiting crossovers between chromosomes as a result of inhibiting MSH5 ***would not prevent spermatogenesis or modulate fertility***. Therefore, these statements, in combination with the teachings of Fishel *et al.* do not provide motivation to administer a compound to a subject *in vivo* which modulates, *e.g.,* inhibits, MSH5 expression or activity. Furthermore, Applicants respectfully submit that Her *et al.* teach that absence of MSH4 or MSH5 has been shown to be associated with an "increased number of nondisjunction of homologous chromosomes at meiosis I." The teachings of Her *et al.* do not imply that inhibition of MSH5 results in infertility. Rather, Her *et al.* teach that inhibition of MSH5 would lead to increased spontaneous abortion due to increased nondisjunction of homologous chromosomes. Furthermore, as stated by the Examiner, the Fishel *et al.* reference does not teach or suggest that the inhibition of MSH5 activity would be useful as contraceptive. Thus, there is no motivation to modify the teachings of Fishel *et al.* to inhibit MSHS expression or activity by contacting MSH5 or a cell expressing MSH5 with a compound, *e.g.,* a small

molecule, or to modulate fertility by contacting MSH5 or a cell expressing MSH5 with a compound, *e.g.*, a small molecule. Furthermore, there is no motivation to modify the teachings of Fishel *et al.* to prevent fertilization or modulate meiosis in a subject by administering an inhibitor of MSH5 expression or activity to the subject.

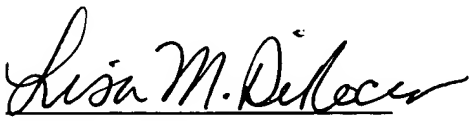
Since the Examiner has not pointed to any teaching or suggestion in the art that would have impelled the ordinarily skilled artisan to modify the cited art to arrive at the methods claimed, it is Applicants' position that the Examiner has used Applicants' invention as a blueprint to combine the references. The CAFC has ruled that "[a] holding that combination claims are invalid based merely upon finding similar elements in separate prior art patents would be 'contrary to statute and would defeat the congressional purpose in enacting Title 35.' " *SmithKline Diagnostics*, 859 F.2d. at 886-887 (citing *Panduit Corp v. Dennison Mfg. Co.*, 810 F.2d 1561, 1577 (Fed. Cir. 1987)) (citations omitted).

In view of the foregoing, Applicants respectfully submit that the combination of Fishel *et al.*, with either Her *et al.* or Baker *et al.* teach or suggest Applicants' invention. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw rejection of the pending claims under 35 U.S.C. §103.

SUMMARY

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' Attorney at (617) 227-7400.

Respectfully submitted,



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Dated: **May 23, 2003**

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 24 and 26-29 have been canceled as being directed to a non-elected invention and claims 22, 30 and 31 have also been canceled, without prejudice.

Claim 15 has been amended as follows:

15. **(Amended)** A method for modulating fertility in a subject ~~MSH5 expression or activity~~ comprising contacting MSH5 or a cell expressing MSH5 with a compound in an amount sufficient ~~a sufficient concentration~~ to modulate MSH5 expression or activity, thereby modulating fertility in a subject.

New claims 32, 33, and 34 have been added as follows:

32. **(New)** A method for inhibiting MSH5 expression or activity in a subject comprising administering to said subject an effective amount of an inhibitor of MSH5 expression or activity, thereby inhibiting MSH5 expression or activity in a subject.

33. **(New)** A method for preventing fertilization in a subject by administering to said subject an effective amount of an inhibitor of MSH5 expression or activity, thereby preventing fertilization in a subject.

34. **(New)** A method for modulating meiosis in a subject comprising administering to said subject an effective amount of an inhibitor of MSH5 expression or activity, thereby modulating meiosis in a subject.

APPENDIX A

15. **(Amended)** A method for modulating fertility in a subject comprising contacting MSH5 or a cell expressing MSH5 with a compound in an amount sufficient to modulate MSH5 expression or activity, thereby modulating fertility in a subject.

16. The method of claim 15, wherein the expression or activity of MSH5 is inhibited.

17. The method of claim 16, wherein said method is used in contraception.

23. The method of claim 15, wherein said compound is capable of modulating MSH5 expression.

25. The method of claim 15, wherein said compound is a small molecule.

32. **(New)** A method for inhibiting MSH5 expression or activity in a subject comprising administering to said subject an effective amount of an inhibitor of MSH5 expression or activity, thereby inhibiting MSH5 expression or activity in a subject.

33. **(New)** A method for preventing fertilization in a subject by administering to said subject an effective amount of an inhibitor of MSH5 expression or activity, thereby preventing fertilization in a subject.

34. **(New)** A method for modulating meiosis in a subject comprising administering to said subject an effective amount of an inhibitor of MSH5 expression or activity, thereby modulating meiosis in a subject.